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(54) Title: METHODS AND COMPOUNDS FOR INHIBITING β -AMYLOID PEPTIDE RELEASE AND/OR ITS SYNTHESIS

(57) Abstract

Disclosed are compounds which inhibit β -amyloid peptide release and/or its synthesis, and, accordingly, have utility in treating Alzheimer's disease. Also disclosed pharmaceutical compositions comprising a compound which inhibits β -amyloid peptide release and/or its synthesis as well as methods for treating Alzheimer's disease both prophylactically and therapeutically with such pharmaceutical compositions.

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METHODS AND COMPOUNDS FOR INHIBITING β -AMYLOID PEPTIDE RELEASE AND/OR ITS SYNTHESIS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of the following U.S. Provisional Applications:

1. U.S. Provisional Application No. 60/____, which was converted pursuant to 37 C.F.R. §1.53(b)(2)(ii) from U.S. Patent Application No. 08/755,442, filed November 22, 1996;
- 5 2. U.S. Provisional Application No. 60/____, which was converted pursuant to 37 C.F.R. §1.53(b)(2)(ii) from U.S. Patent Application No. 08/808,528, filed February 28, 1997;
- 10 3. U.S. Provisional Application No. 60/____, which was converted pursuant to 37 C.F.R. §1.53(b)(2)(ii) from U.S. Patent Application No. 08/807,528, filed February 28, 1997; and
- 15 4. U.S. Provisional Application No. 60/____, which was converted pursuant to 37 C.F.R. §1.53(b)(2)(ii) from U.S. Patent Application No. 08/807,427, filed February 28, 1997.

Each of these applications are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

20 Field of the Invention

This invention relates to methods which inhibit cellular β -amyloid peptide release and/or its synthesis, and, accordingly, have utility in treating Alzheimer's disease. This invention also relates to pharmaceutical compositions comprising such compounds as well as methods for inhibiting release of
25 β -amyloid peptide.

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References

10 The following publications, patents and patent applications are cited in this application as superscript numbers:

- 15 1 Glennner, et al., "Alzheimer's Disease: Initial Report of the Purification and Characterization of a Novel Cerebrovascular Amyloid Protein", *Biochem. Biophys. Res. Commun.*, 120:885-890 (1984).
- 20 2 Glennner, et al., "Polypeptide Marker for Alzheimer's Disease and its Use for Diagnosis", *U.S. Patent No. 4,666,829* issued May 19, 1987.
- 25 3 Selkoe, "The Molecular Pathology of Alzheimer's Disease", *Neuron*, 6:487-498 (1991).
- 30 4 Goate, et al., "Segregation of a Missense Mutation in the Amyloid Precursor Protein Gene with Familial Alzheimer's Disease", *Nature*, 349:704-706 (1990).
- 35 5 Chartier-Harlan, et al., "Early-Onset Alzheimer's Disease Caused by Mutations at Codon 717 of the β -Amyloid Precursor Protein Gene", *Nature*, 353:844-846 (1989).
- 6 Murrell, et al., "A Mutation in the Amyloid Precursor Protein Associated with Hereditary Alzheimer's Disease", *Science*, 254:97-99 (1991).
- 7 Mullan, et al., "A Pathogenic Mutation for Probable Alzheimer's Disease in the APP Gene at the N-Terminus of β -Amyloid", *Nature Genet.*, 1:345-347 (1992).

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8 Schenk, et al., "Methods and Compositions for the Detection of Soluble β -Amyloid Peptide", *International Patent Application Publication No. WO 94/10569*, published 11 May 1994.

5 9 Selkoe, "Amyloid Protein and Alzheimer's Disease", *Scientific American*, pp. 2-8, November, 1991.

10 10 Losse, et al., *Tetrahedron*, 27:1423-1434 (1971).

10 11 Citron, et al., "Mutation of the β -Amyloid Precursor Protein in Familial Alzheimer's Disease Increases β -Protein Production", *Nature*, 360:672-674 (1992).

15 12 Hansen, et al., "Reexamination and Further Development of a Precise and Rapid Dye Method for Measuring Cell Growth/Cell Kill", *J. Immun. Meth.*, 119:203-210 (1989).

13 P. Seubert, *Nature* (1992) 359:325-327

20 14 Johnson-Wood et al., *PNAS USA* (1997) 94:1550-1555

15 15 *Tetrahedron Letters*, 34(48), 7685 (1993))

25 All of the above publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

30

State of the Art

Alzheimer's Disease (AD) is a degenerative brain disorder characterized clinically by progressive loss of memory, cognition, reasoning, judgment and emotional stability that gradually leads to profound mental deterioration and ultimately death. AD is a very common cause of progressive mental failure (dementia) in aged humans and is believed to represent the fourth most common medical cause of death in the United States. AD has been observed in races and ethnic groups worldwide and presents a major present and future public health problem. The disease is currently estimated to affect about two to three

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million individuals in the United States alone. AD is at present incurable. No treatment that effectively prevents AD or reverses its symptoms and course is currently known.

5 The brains of individuals with AD exhibit characteristic lesions termed senile (or amyloid) plaques, amyloid angiopathy (amyloid deposits in blood vessels) and neurofibrillary tangles. Large numbers of these lesions, particularly amyloid plaques and neurofibrillary tangles, are generally found in several areas of the human brain important for memory and cognitive function
10 in patients with AD. Smaller numbers of these lesions in a more restrictive anatomical distribution are also found in the brains of most aged humans who do not have clinical AD. Amyloid plaques and amyloid angiopathy also characterize the brains of individuals with Trisomy 21 (Down's Syndrome) and Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch Type (HCHWA-D). At present, a definitive diagnosis of AD usually requires observing the aforementioned lesions in the brain tissue of patients who have died with the disease or, rarely, in small biopsied samples of brain tissue taken during an invasive neurosurgical procedure.

20 The principal chemical constituent of the amyloid plaques and vascular amyloid deposits (amyloid angiopathy) characteristic of AD and the other disorders mentioned above is an approximately 4.2 kilodalton (kD) protein of about 39-43 amino acids designated the β -amyloid peptide (β AP) or sometimes A β , A β P or β /A4. β -Amyloid peptide was first purified and a partial amino acid sequence was provided by Glenner, et al.¹ The isolation procedure and the sequence data for the first 28 amino acids are described in U.S. Patent No. 4,666,829².

30 Molecular biological and protein chemical analyses have shown that the β -amyloid peptide is a small fragment of a much larger precursor protein (APP), that is normally produced by cells in many tissues of various animals,

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including humans. Knowledge of the structure of the gene encoding the APP has demonstrated that β -amyloid peptide arises as a peptide fragment that is cleaved from APP by protease enzyme(s). The precise biochemical mechanism by which the β -amyloid peptide fragment is cleaved from APP and subsequently deposited as amyloid plaques in the cerebral tissue and in the walls of the 5 cerebral and meningeal blood vessels is currently unknown.

Several lines of evidence indicate that progressive cerebral deposition of β -amyloid peptide plays a seminal role in the pathogenesis of AD and can 10 precede cognitive symptoms by years or decades. See, for example, Selkoe³. The most important line of evidence is the discovery that missense DNA mutations at amino acid 717 of the 770-amino acid isoform of APP can be found in affected members but not unaffected members of several families with a genetically determined (familial) form of AD (Goate, et al.⁴; Chartier-Harlan, 15 et al.⁵; and Murrell, et al.⁶) and is referred to as the Swedish variant. A double mutation changing lysine⁵⁹⁵-methionine⁵⁹⁶ to asparagine⁵⁹⁵-leucine⁵⁹⁶ (with reference to the 695 isoform) found in a Swedish family was reported in 1992 (Mullan, et al.⁷). Genetic linkage analyses have demonstrated that these 20 mutations, as well as certain other mutations in the APP gene, are the specific molecular cause of AD in the affected members of such families. In addition, a mutation at amino acid 693 of the 770-amino acid isoform of APP has been identified as the cause of the β -amyloid peptide deposition disease, HCHWA-D, and a change from alanine to glycine at amino acid 692 appears to cause a 25 phenotype that resembles AD in some patients but HCHWA-D in others. The discovery of these and other mutations in APP in genetically based cases of AD prove that alteration of APP and subsequent deposition of its β -amyloid peptide fragment can cause AD.

Despite the progress which has been made in understanding the 30 underlying mechanisms of AD and other β -amyloid peptide related diseases, there remains a need to develop methods and compositions for treatment of the

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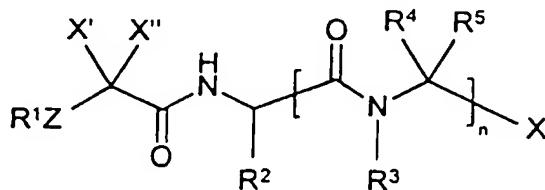
disease(s). Ideally, the treatment methods would advantageously be based on drugs which are capable of inhibiting β -amyloid peptide release and/or its synthesis *in vivo*.

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SUMMARY OF THE INVENTION

This invention is directed to the discovery of a class of compounds which inhibit β -amyloid peptide release and/or its synthesis and, therefore, are useful in the prevention of AD in patients susceptible to AD and/or in the treatment of patients with AD in order to inhibit further deterioration in their condition. The class of compounds having the described properties are defined by formula I below:

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I

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wherein R¹ is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, aryl, heteroaryl and heterocyclic;

R² is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclic;

each R³ is independently selected from the group consisting of hydrogen and methyl and R³ together with R⁴ can be fused to form a cyclic structure of from 3 to 8 atoms which is optionally fused with an aryl or heteroaryl group;

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each R⁴ is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, heteroaryl, heterocyclic, substituted alkyl, substituted alkenyl and substituted alkynyl;

each R⁵ is selected from hydrogen and methyl or together with R⁴ forms a cycloalkyl group of from 3 to 6 carbon atoms;

X is selected from the group consisting of -C(O)Y and -C(S)Y where Y is selected from the group consisting of

- (a) alkyl or cycloalkyl,
- (b) substituted alkyl with the proviso that the substitution on said substituted alkyl do not include α -haloalkyl, α -diazoalkyl, α -OC(O)alkyl, or α -OC(O)aryl groups,
- (c) alkoxy or thioalkoxy,
- (d) substituted alkoxy or substituted thioalkoxy,
- (e) hydroxy,
- (f) aryl,
- (g) heteroaryl,
- (h) heterocyclic,
- (i) -NR'R" where R' and R" are independently selected from hydrogen, alkyl, alkenyl, alkynyl, substituted alkyl, substituted alkenyl, substituted alkenyl, cycloalkyl, aryl, heteroaryl, heterocyclic, where one of R' or R" is hydroxy or alkoxy, and where R' and R" are joined to form a cyclic group having from 2 to 8 carbon atoms optionally containing 1 to 2 additional heteroatoms selected from oxygen, sulfur and nitrogen and optionally substituted with one or more alkyl, alkoxy or carboxylalkyl groups,
- (j) -NHSO₂-R⁸ where R⁸ is selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, aryl, heteroaryl and heterocyclic,
- (k) -NR⁹NR¹⁰R¹⁰ where R⁹ is hydrogen or alkyl, and each R¹⁰ is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, aryl, heteroaryl, heterocyclic, and
- (l) -ONR⁹[C(O)O]_zR¹⁰ where z is zero or one, R⁹ and R¹⁰ are as defined above;

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X can also be $-CR^6R^6Y'$ where each R^6 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl and heterocyclic and Y' is selected from the group consisting of hydroxyl, amino, thiol, alkoxy, substituted alkoxy, thioalkoxy, substituted thioalkoxy, $-OC(O)R^7$, $-SSR^7$, $-SSC(O)R^7$ where R^7 is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl and heterocyclic,

5 X' is hydrogen, hydroxy, or fluoro;
X" is hydrogen, hydroxy or fluoro, or X' and X" together form an oxo
10 group;

Z is selected from the group consisting of a bond covalently linking R^1 to $-CX'X''-$, oxygen and sulfur;

n is an integer equal to 1 or 2; and
pharmaceutically acceptable salts thereof
15 with the provisos that:

A. when R^1 is phenyl or 3-nitrophenyl, R^2 is methyl, R^3 is hydrogen, R^4 is $-CH(OH)CH_3$, R^5 is hydrogen, X' and X" are hydrogen, Z is a bond, and n is 1, then X is not $-C(O)OH$;
B. when R^1 is phenyl, R^2 is methyl, R^3 is hydrogen, R^4 is $-CH(OH)CH_3$,
20 derived from D-threonine, R^5 is hydrogen, X' and X" are hydrogen, Z is a bond, and n is 1, then X is not $-C(O)OH$ or $-C(O)OCH_3$;

C. when R^1 is phenyl, R^2 is methyl, R^4 is benzyl, R^5 is hydrogen, X is methoxycarbonyl, X' and X" are hydrogen, Z is a bond, and n is 1, then R^3 is not methyl;

D. when R^1 is iso-propyl, R^2 is $-CH_2C(O)NH_2$, R^3 is hydrogen, R^4 is iso-butyl, R^5 is hydrogen, X' and X" are hydrogen, Z is a bond, and n is 1, then X is not $-C(O)OCH_3$;

E. when R^1 is phenyl, R^2 is methyl, R^5 is hydrogen, X is $-C(O)OCH_3$, X' and X" are hydrogen, Z is a bond, and n is 1, then R^3 , the nitrogen atom attached to R^3 , and R^4 do not form 1,2,3,4-tetrahydroiso-quinolin-2-yl or pyrrolidin-2-yl;

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F. when R¹ is phenyl, R² is methyl, R³ is hydrogen, R⁵ is hydrogen, X is -C(O)OCH₃, X' and X" are hydrogen, Z is a bond, and n is 1, then R⁴ is not 4-amino-n-butyl;

5 G. when R¹ is 3-nitrophenyl, R² is methyl, R³ is hydrogen, R⁴ is -CH(OH)CH₃, R⁵ is hydrogen, X' and X" are hydrogen, Z is a bond, and n is 1, then X is not -C(O)NH₂ or -CH₂OH;

H. when R¹ is phenyl, R² is methyl, R³ is hydrogen, R⁵ is hydrogen, X is -CH₂OCH₃, X' and X" are hydrogen, Z is a bond, and n is 1, then R⁴ is not benzyl or ethyl;

10 I. when R¹ is 3,5-difluorophenyl, R² is methyl, R³ is methyl, R⁴ is methyl, R⁵ is hydrogen, X' and X" are hydrogen, Z is a bond, and n is 1, then X is not -CHOHφ;

J. when R¹ is 3,5-difluorophenyl, R² is methyl, R³ is hydrogen, R⁴ is phenyl derived from D-phenylglycine, R⁵ is hydrogen, X' and X" are 15 hydrogen, Z is a bond, and n is 1, then X is not -CHOHφ or -CH₂OH;

K. when R₁ is N-(2-pyrrolidinonyl), R₂ is methyl, R₃ is hydrogen, R₄ is benzyl, R⁵ is hydrogen, X' and X" are hydrogen, Z is a bond, and n is 1, then X is not -C(O)OCH₃;

20 L. when R¹ is 3,5-difluorophenyl, R² is methyl derived from D-alanine, R³ is hydrogen, R⁴ is phenyl derived from D-phenylglycine, R⁵ is hydrogen, X' and X" are hydrogen, Z is a bond, and n is 1, then X is not -C(O)NH-benzyl;

M. when R¹ is 3,5-difluorophenyl, R² is methyl, R³ is hydrogen, R⁴ is hydrogen, R⁵ is hydrogen, X' and X" are hydrogen, Z is a bond, and n is 1, then X is not -CH₂OH;

25 N. when R¹ is 3,5-difluorophenyl, R² is methyl, R³ is hydrogen, R⁴ is 4-phenylphenyl, R⁵ is hydrogen, X' and X" are hydrogen, Z is a bond, and n is 1, then X is not -C(O)NHC(CH₃)₃; and

O. when R¹ is 3,5-difluorophenyl, R² is methyl, R³ is hydrogen, R⁴ is phenyl derived from D-phenylglycine, R⁵ is hydrogen, X' and X" are 30 hydrogen, Z is a bond, and n is 1, then X is not -C(O)NHCH(CH₃)φ.

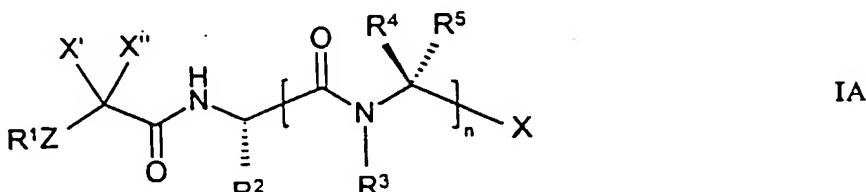
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Preferably, the compounds of this invention are derived from L-amino acids and, accordingly, are represented by formula IA:

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IA

Accordingly, in one of its method aspects, this invention is directed to a method for inhibiting β -amyloid peptide release and/or its synthesis in a cell which method comprises administering to such a cell an amount of a compound or a mixture of compounds of formula I above effective in inhibiting the cellular release and/or synthesis of β -amyloid peptide.

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Because the *in vivo* generation of β -amyloid peptide is associated with the pathogenesis of AD^{8,9}, the compounds of formula I can also be employed in conjunction with a pharmaceutical composition to prophylactically and/or therapeutically prevent and/or treat AD. Accordingly, in another of its method aspects, this invention is directed to a prophylactic method for preventing the onset of AD in a patient at risk for developing AD which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically inert carrier and an effective amount of a compound or a mixture of compounds of formula I above.

In yet another of its method aspects, this invention is directed to a therapeutic method for treating a patient with AD in order to inhibit further deterioration in the condition of that patient which method comprises

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administering to said patient a pharmaceutical composition comprising a pharmaceutically inert carrier and an effective amount of a compound or a mixture of compounds of formula I above.

5 Compounds suitable for use in the claimed methods include, by way of example only, the following:

10 *N-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-(S)-2-aminohexanoate methyl ester*

15 *N-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-L-histidine methyl ester*

20 *N-benzyl-N'-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-(S)-2-aminohexanamide*

25 *N-2-(N,N-dimethylamino)ethyl-N'-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-(S)-2-aminohexanamide*

30 *N-(2-methoxyethyl)-N'-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-(S)-2-aminohexanamide*

35 *N-2-(N,N-dimethylamino)ethyl-N'-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylalaninamide*

40 *N-(4-pyridyl)methyl-N'-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylalaninamide*

45 *N-(3-pyridyl)methyl-N'-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylalaninamide*

50 *N-(4-pyridyl)methyl-N'-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-(S)-2-aminohexanamide*

55 *N-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-(S)-2-aminohexanoate *tert*-butyl ester*

60 *N-[N-(pent-4-enoyl)-L-alaninyl]-L-phenylalanine methyl ester*

65 *N-[N-(dec-4-enoyl)-L-alaninyl]-L-phenylalanine methyl ester*

70 *N-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-L-4-[3-(N,N-dimethylamino)propoxy]phenylalanine methyl ester*

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5 *N-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-L-4-[(tert-butyloxycarbonyl)methoxy]phenylalanine methyl ester*

10 *N-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-L-tyrosine methyl ester*

15 *N-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-L-4-(2-morpholinoethoxy)phenylalanine methyl ester*

20 *N-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-(S)-2-amino-6-(N,N-dimethylamino)hexanoate methyl ester*

25 *N-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-(S)-2-amino-3-(2-pyridyl)propionate methyl ester*

30 *N-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-(S)-2-amino-3-(3-pyridyl)propionate methyl ester*

35 *N-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-L-proline methyl ester*

40 *1-[N-(3,5-difluorophenylacetyl)-L-alaninyl]piperidine-2-carboxylate methyl ester*

45 *N-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-L-4-(2-methoxyethyl)-N'-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-L-4-(2-morpholinoethoxy)phenylalaninamide*

N-(2-methoxyethyl)-N'-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-3-methoxypropionamide

N-[N-(3,5-difluorophenylacetyl)-L-alaninyl]glycine methyl ester

N-(2-methoxyethyl)-N'-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-3-(4-pyridyl)propionamide

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5 *N*-(2-methoxyethyl)-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-3-(2-pyridyl)propionamide

10 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-(S)-2-amino-3-(thiazol-4-yl)propionate methyl ester

15 2-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate methyl ester

20 *N*-(3-methoxybenzyl)-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylalaninamide

25 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-(S)-2-amino-3-(1-naphthyl)propionate methyl ester

30 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-(S)-2-amino-3-(2-thienyl)propionate methyl ester

35 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylalanine benzyl ester

40 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylalanine 3-bromo-propyl ester

45 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylalanine 3-iodopropyl ester

50 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-leucine *tert*-butyl ester

55 *N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-2-(2-pyridyl)acetamide

60 *N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-2-(3-pyridyl)acetamide

65 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-*N*-(*tert*-butoxycarbonyl)-L-lysine methyl ester

70 methyl *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-(S)-2-amino-4-phenylbutanoate

75 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]glycine 2-phenylethyl ester

80 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]glycine 3-phenylpropyl ester

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5 *N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-2-(4-pyridyl)acetamide

10 *N*-[*N*-(phenylacetyl)-L-alaninyl]-L-threonine methyl ester

15 *N'*-[*N*-(phenylacetyl)-L-alaninyl]-L-leucinamide

20 *N'*-[*N*-(phenylacetyl)-L-alaninyl]-L-alaninamide

25 *N'*-[*N*-(phenylacetyl)-L-alaninyl]-L-phenylalaninamide

30 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-2-(3-pyridyl)acetate ethyl ester

35 *N*-methyl-*N'*-[*N*-(phenylacetyl)-L-alaninyl]-L-leucinamide

40 *N,N*-dimethyl-*N'*-[*N*-(phenylacetyl)-L-alaninyl]-L-phenylalaninamide

45 *N,N*-dimethyl-*N'*-[*N*-(phenylacetyl)-L-alaninyl]-L-leucinamide

50 *N,N*-dimethyl-*N'*-[*N*-(phenylacetyl)-L-alaninyl]-L-valinamide

55 *N*-methyl-*N'*-[*N*-(phenylacetyl)-L-alaninyl]-L-phenylalaninamide

60 *N*-methyl-*N'*-[*N*-(phenylacetyl)-L-alaninyl]-L-valinamide

65 *N*-methyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-(S)-2-aminohexanamide

70 *N,N*-dimethyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-(S)-2-aminohexanamide

75 *N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-(S)-2-aminohexanamide

80 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-2-(3-methoxyphenyl)acetate methyl ester

85 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-2-(4-methoxyphenyl)acetate methyl ester

90 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-2-(2-pyridyl)acetate ethyl ester

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5 *N-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-2-(4-pyridyl)acetate ethyl ester*

10 *N-[N-(cyclohexylacetyl)-L-alaninyl]-L-phenylalanine methyl ester*

15 *N-[N-(cyclopentylacetyl)-L-alaninyl]-L-phenylalanine methyl ester*

20 *N-[N-(cyclohex-1-enylacetyl)-L-alaninyl]-L-phenylalanine methyl ester*

25 *N-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-1-aminocyclopropane-1-carboxylate methyl ester*

30 *N-2-(*N,N*-dimethylamino)ethyl-*N*-methyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninamide*

35 *N-[N-(cyclopropylacetyl)-L-alaninyl]-L-phenylalanine methyl ester*

40 *N-[N-(3,5-difluorophenylacetyl)-L-alaninyl]glycine benzyl ester*

45 *N-[N-(isovaleryl)-L-phenylglycanyl]-L-alanine ethyl ester*

50 *N-[N-(3-nitrophenylacetyl)-L-alaninyl]-L-phenylalanine methyl ester*

55 *N-[N-(3-nitrophenylacetyl)-L-alaninyl]-L-alanine ethyl ester*

60 *N-[N-(3-nitrophenylacetyl)-L-alaninyl]glycine ethyl ester*

65 *N-hydroxy-*N'*-[*N*-(3-nitrophenylacetyl)-L-alaninyl]-D,L-threoninamide*

70 *N-[N-(isovaleryl)-L-phenylglycanyl]-L-alanine *iso*-butyl ester*

75 *N-[N-(3-nitrophenylacetyl)-L-alaninyl]-2-amino-3-(3-hydroxyphenyl)propionate methyl ester*

80 *N-[N-(3-nitrophenylacetyl)-L-alaninyl]-L-tyrosine ethyl ester*

85 *N-[N-(isovaleryl)-L-isoleucanyl]-L-alanine *iso*-butyl ester*

90 *N-[N-[*N*-(isovaleryl)-L-valinyl]-L-phenylglycanyl]-L-alanine *iso*-butyl ester*

95 *N-[N-(isovaleryl)-L-phenylalaninyl]-L-alanine *iso*-butyl ester*

100 *N-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alanine ethyl ester*

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1-[*N*-(3-nitrophenylacetyl)-L-alaninyl]-indoline-(S)-2-carboxylate ethyl ester

5 *N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninamide

N-methoxy-*N*-methyl-*N'*-[*N*-(isovaleryl)-L-phenylglycanyl]-L-alaninamide

N-iso-butyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninamide

10 *N,N*-di-*n*-propyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninamide

N'-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-valinamide

15 *N*-(4-nitrophenyl)-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninamide

N'-[*N*-[*N*-(isovaleryl)-L-phenylglycanyl]-L-alaninyl]-L-phenylalaninamide

20 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylalanine methyl ester

N'-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylalaninamide

N-iso-butyl-*N'*-[*N*-(isovaleryl)-L-phenylglycanyl]-L-alaninamide

25 *N*-(2-methoxyethyl)-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylalaninamide

N-(4-nitrobenzyl)-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninamide

30 *N*-(4-nitrophenyl)-*N'*-[*N*-[*N*-(isovaleryl)-L-phenylglycanyl]-L-alaninyl]-L-alaninamide

N-(4-nitrophenyl)-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylalaninamide

35 *N*-(4-nitrophenyl)-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylalaninamide

N-benzyl-*N*-methyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninamide

40 *N*-(3,5-difluorobenzyl)-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninamide

N-(3-nitrobenzyl)-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninamide

45 *N*-(3-nitrobenzyl)-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninamide

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5 *N*-benzyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninamide

10 *N*-(4-nitrobenzyl)-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylalaninamide

15 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-tryptophan methyl ester

20 *N*-(4-methoxybenzyl)-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninamide

25 *N*-[*N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylalaninyl]-L-phenylglycine methyl ester

30 *N*-[*N*-(cyclohexylacetyl)-L-phenylglyciny]-L-alanine ethyl ester

35 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylglycine methyl ester

40 *N*-[*N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninyl]-L-phenylglycine methyl ester

45 *N*-(2-phenylethyl)-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninamide

50 *N*'-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-tryptophanamide

55 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-(*S*)-2-amino-3-cyclohexylpropionate methyl ester

60 *N*-(2-methoxethyl)-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-(*S*)-2-amino-3-(4-nitrophenyl)propionamide

65 *N*-[*N*-(3-nitrophenylacetyl)-L-alaninyl]-L-serine ethyl ester

70 *N*-[(*R*)- α -methylbenzyl]-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninamide

75 *N*-[(*S*)- α -methylbenzyl]-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninamide

80 *N*-(4-fluorobenzyl)-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninamide

85 *N*-(4-pyridylmethyl)-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninamide

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N-(4-trifluoromethylbenzyl)-N'-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninamide
5 N-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-2-phenylpropionate
 ethyl ester
10 N-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylalanine *tert*-butyl
 ester
15 N-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-2-methylpropionate
 methyl ester
20 N-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-2-cyclohexylacetate
 ethyl ester
25 N-(2-methoxyethyl)-N'-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-L-
 phenylglycinamide
30 N-[N-(isovaleryl)-2-amino-2-cyclohexylacetyl]-L-alanine ethyl ester
 N-2-(*N,N*-dimethylamino)ethyl-N'-[N-(3,5-difluorophenylacetyl)-L-
 alaninyl]-L-phenylglycinamide
35 N-(2-pyridylmethyl)-N'-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-L-
 phenylglycinamide
40 N-[N-(3-pyridylacetyl)-L-alaninyl]-L-phenylalanine methyl ester
 N-[N-(2-pyridylacetyl)-L-alaninyl]-L-phenylalanine methyl ester
 N-[N-(4-pyridylacetyl)-L-alaninyl]-L-phenylalanine methyl ester
 N-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-2-(4-
 fluorophenyl)acetate ethyl ester
45 N-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-2-(2-
 fluorophenyl)acetate ethyl ester
 N-[N-(3,5-difluorophenylacetyl)-L-phenylglycyl]-L-alanine ethyl ester
 N-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-3-
 phthalimidopropionate ethyl ester
 N-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylglycine neopentyl
 ester

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5 *N*-*tert*-butyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylglycinamide

10 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylglycine *tert*-butyl ester

15 *N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylglycinamide

20 4-[*N*-[*N*-(3-nitrophenylacetyl)-L-alaninyl]-L-valinyl]morpholine

25 *N*-[*N*-(3-nitrophenylacetyl)-L-alaninyl]-L-valine ethyl ester

30 *N*-[*N*-(3-nitrophenylacetyl)-L-alaninyl]-L-threonine methyl ester

35 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-(*S*)-2-aminopentanoate methyl ester

40 4-[*N*-[*N*-(3-nitrophenylacetyl)-L-alaninyl]-(*S*)-2-amino-3-*tert*-butoxybutyryl]morpholine

45 4-[*N*-[*N*-(3-nitrophenylacetyl)-L-alaninyl]-L-isoleucinyl]morpholine

50 *N*-[*N*-(3-nitrophenylacetyl)-L-alaninyl]-L-isoleucine methyl ester

55 *N*-[*N*-(3-nitrophenylacetyl)-L-alaninyl]-L-isoleucine

60 *N*-[*N*-[*N*-(3-nitrophenylacetyl)-L-alaninyl]-L-threoninyl]-L-valine ethyl ester

65 *N*-[*N*-(3-nitrophenylacetyl)-L-alaninyl]-(*S*)-2-aminopentanoate methyl ester

70 *N*-[*N*-(3-nitrophenylacetyl)-L-alaninyl]-L-leucine methyl ester

75 *N*-2-methoxyethyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninamide

80 *N*-2-(*N,N*-dimethylamino)ethyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninamide

85 *N*-cyclohexyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninamide

90 *N*-neopentyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninamide

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5 *N*-tetrahydrofurfuryl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninamide

10 *N*-2-pyridylmethyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninamide

15 3-[*N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninyl]thiazolidine

20 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-(*S*)-2-aminobutanoate methyl ester

25 *N*-[*N*-(3-nitrophenylacetyl)-L-alaninyl]-(*S*)-2-aminobutanoate methyl ester

30 *N*-(R)-*sec*-butyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninamide

35 1-[*N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninyl]pyrrolidine

40 *N*-(S)-*sec*-butyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninamide

45 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-valine methyl ester

50 *N*-2-fluoroethyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninamide

55 *N*-[(S)-6-methyl-3-oxohept-2-yl]-*N'*-(3,5-difluorophenylacetyl)-L-alaninamide

60 *N*-4-nitrobenzyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-(*S*)-2-aminobutyramide

65 *N*-4-nitrobenzyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-(*S*)-2-aminopentanamide

70 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-2-(3-fluorophenyl)acetate methyl ester

75 *N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-(*S*)-2-amino-2-(2-thienyl)acetamide

80 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-2-(5-chlorobenzothiophen-2-yl)acetate methyl ester

85 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-2-(benzothiophen-2-yl)acetate ethyl ester

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5 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-2-(benzothiophen-3-yl)acetate methyl ester

10 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-2-(2-thienyl)acetate methyl ester

15 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-2-(benzothiophen-5-yl)acetate ethyl ester

20 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-(S)-2-amino-2-(2-thienyl)acetate methyl ester

25 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-(S)-2-amino-2-(2-thienyl)acetate *tert*-butyl ester

30 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-(S)-2-amino-2-(2-thienyl)acetic acid

35 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-2-(1*H*-tetrazol-5-yl)acetate methyl ester

40 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-2-(6-methoxy-2-naphthyl)acetate methyl ester

45 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-2-(3-trifluoromethylphenyl)acetate methyl ester

50 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-2-(4,5,6,7-tetrahydrobenzothiophen-2-yl)acetate methyl ester

55 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-2-(thieno[2,3-*b*]thiophen-2-yl)acetate methyl ester

60 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-2-(2-methylthiazol-4-yl)acetate methyl ester

65 (3*S*,4*S*)-*N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-4-amino-3-hydroxy-5-phenylpentanoate methyl ester

70 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-2-(2-methylthiazol-4-yl)acetate methyl ester

75 *N*-[*N*-(cyclopropylacetyl)-L-alaninyl]-L-phenylglycine *tert*-butyl ester

80 *N*-*tert*-butyl-*N*'-[*N*-(3,5-Difluorophenylacetyl)-L-alaninyl]-(S)-2-amino-2-(4-phenylphenyl)acetamide

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5 *N*-[*N*-(3,5-difluorophenylacetyl)-(S)-2-aminobutanoyl]-L-phenylglycine
 tert-Butyl Ester

10 *N*-[*N*-(3,5-difluorophenylacetyl)-L-valinyl]-L-phenylglycine *tert*-butyl
 ester

15 *N*-[*N*-(3,5-difluorophenylacetyl)-L-methioninyl]-L-phenylglycine methyl
 ester

20 *N*-[*N*-(3,5-difluorophenylacetyl)-L-valinyl]-L-phenylglycine methyl ester

25 *N*-[*N*-(3,5-difluorophenylacetyl)-2-aminobutanoyl]-L-phenylglycine
 methyl ester

30 *N*-[*N*-(3,5-difluorophenylacetyl)-L-leucinyl]-L-phenylglycine methyl ester

35 *N*-[*N*-(3,5-difluorophenylacetyl)-L-phenylalaninyl]-L-phenylglycine
 methyl ester

40 *N*-[*N*-(phenylacetyl)-L-alaninyl]-L-alanine methyl ester

45 *N*-[*N*-(phenylacetyl)-L-alaninyl]-L-leucine methyl ester

50 *N*-[*N*-(phenylacetyl)-L-alaninyl]-L-isoleucine methyl ester

55 *N*-[*N*-(phenylacetyl)-L-alaninyl]-L-proline methyl ester

60 *N*-[*N*-(phenylacetyl)-L-alaninyl]-L-phenylalanine methyl ester

65 *N*-[*N*-(phenylacetyl)-L-alaninyl]-*N*-(*tert*-butoxycarbonyl)-L-lysine methyl
 ester

70 *N*-[*N*-(phenylacetyl)-L-alaninyl]-glycine methyl ester

75 *N*-[*N*-(phenylacetyl)-L-alaninyl]-L-valine methyl ester

80 *N*-[*N*-(phenylacetyl)-L-alaninyl]-(S)-2-aminobutanoate methyl ester

85 *N*-[*N*-(phenylacetyl)-L-alaninyl]-(S)-2-aminopentanoate methyl ester

90 *N*-[*N*-(3-nitrophenylacetyl)-L-alaninyl]-L-valine

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N-[*N*-(phenylacetyl)-L-alaninyl]-L-*N*-methylalanine methyl ester

N-[*N*-(isovaleryl)-L-phenylglycinyl]-L-alanine *iso*-butyl ester

5 *N*-[*N*-(isovaleryl)-L-isoleucinyl]-L-alanine *iso*-butyl ester

N-Cyclohexyl-*N*'-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylglycinamide

10 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-4-hydroxyproline ethyl ester

N-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-lysine methyl ester

15 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-glutamide

 1-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]piperidine-2-carboxylate methyl ester

20 *N*-[(S)-3-hydroxy-6-methylhept-2-yl]-*N*'-(3,5-difluorophenylacetyl)-L-alaninamide

N-[(S)-2-hydroxy-1-phenyleth-1-yl]-*N*'-(3,5-difluorophenylacetyl)-L-alaninamide

25 *N*-[*N*-(3,5-difluorophenyl- α -fluoroacetyl)-L-alaninyl]-L-phenylglycine *tert*-butyl ester

30 *N*-[*N*-(3,5-difluorophenylacetyl)-2-(S)-aminocyclohexylacetyl]-L-phenylglycine methyl ester

N-[(1R,2S)-1-hydroxy-1-phenylprop-2-yl]-*N*'-(3,5-difluorophenylacetyl)-L-alaninamide

35 *N*-[(1R,2S)-1-hydroxy-1,2-diphenyleth-2-yl]-*N*'-(3,5-difluorophenylacetyl)-L-alaninamide

N-[(1S,2R)-1-hydroxy-1-phenylprop-2-yl]-*N*'-(3,5-difluorophenylacetyl)-L-alaninamide

40 *N*-2-methoxyethyl-*N*'-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-glycinamide

N-[(S)- α -hydroxy- α -phenyl-*iso*-propyl]-*N*'-(3,5-difluorophenylacetyl)-L-alaninamide

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5 *N*-[(S)-2-hydroxy-1,2-diphenylethyl]-*N'*-(3,5-difluorophenylacetyl)-L-alaninamide

10 *N*-[(S)-1-hydroxyhex-2-yl]-*N'*-(3,5-difluorophenylacetyl)-L-alaninamide

15 *N*-[α -hydroxy- α' -(4-hydroxyphenyl)-*iso*-propyl]-*N'*-(3,5-difluorophenylacetyl)-L-alaninamide

20 *N*-2-pyridylmethyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylalaninamide

25 *N*-[α -hydroxy- α' -pyrid-2-yl-*iso*-propyl]-*N'*-(3,5-difluorophenylacetyl)-L-alaninamide

30 *N*-[α -hydroxy- α' -pyrid-4-yl-*iso*-propyl]-*N'*-(3,5-difluorophenylacetyl)-L-alaninamide

35 *N*-[(S)-1-hydroxy-4-methylpent-2-yl]-*N'*-(3,5-difluorophenylacetyl)-L-alaninamide

40 *N*-[α -methoxy-prop-2-yl]-*N'*-(3,5-difluorophenylacetyl)-L-alaninamide

45 *N*-[1-hydroxy-3-methyl-but-2-yl]-*N'*-(3,5-difluorophenylacetyl)-L-alaninamide

50 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-2-(6-aminopyrid-2-yl)acetate methyl ester

55 *N*-[1-hydroxy-prop-2-yl]-*N'*-(3,5-difluorophenylacetyl)-L-alaninamide

60 *N*-[(S)-2-methoxy-1-phenyleth-1-yl]-*N'*-(3,5-difluorophenylacetyl)-L-alaninamide

65 *N*-[(S)-1-methoxy-2-phenyl-prop-2-yl]-*N'*-(3,5-difluorophenylacetyl)-L-alaninamide

70 *N*-[(S)-1-acetoxyhex-2-yl]-*N'*-(3,5-difluorophenylacetyl)-L-alaninamide

75 *N*-[(S)-1-(*tert*-butylcarbonyloxy)-hex-2-yl]-*N'*-(3,5-difluorophenylacetyl)-L-alaninamide

80 *N*-[2-hydroxy-1-(thien-2-yl)ethyl]-*N'*-(3,5-difluorophenylacetyl)-L-alaninamide

85 *N*-[(S)-2-hydroxy-2-methyl-1-phenylprop-1-yl]-*N'*-(3,5-difluorophenylacetyl)-L-alaninamide

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5 *N*-[*N*-(3,5-difluorophenylacetyl)-L-(thien-2-yl)glyciny]-L-phenylalanine
tert-butyl ester

10 *N*-[*N*-(3,5-difluorophenylacetyl)-L-phenylglyciny]-L-phenylglycinol

15 *N*-[*N*-(cyclopropaneacetyl)-L-phenylglyciny]-L-phenylglycinol

20 *N*-[*N*-(cyclopentaneacetyl)-L-phenylglyciny]-L-phenylglycinol

25 *N*-[*N*-(3,5-difluorophenylacetyl)-D,L-phenylglyciny]-D,L-phenylglycinamide

30 *N*-[*N*-(3,5-difluorophenylacetyl)-D,L-valinyl]-D,L-phenylglycinamide

35 *N*-[*N*-(2-thienylacetyl)-L-alaninyl]-L-phenylglycinamide

40 *N*-[*N*-(*n*-caprotyl)-L-alaninyl]-L-phenylglycinamide

45 *N*-[*N*-(3,5-difluorophenylacetyl)-L-norleucinyl]-L-phenylglycine methyl ester

50 *N*-[*N*-(3,5-difluorophenylacetyl)-L-norvalinyl]-L-phenylglycine methyl ester

55 *N*-[*N*-(3,5-difluorophenylacetyl)-L-*tert*-leucinyl]-L-phenylglycine methyl ester

60 *N*-[*N*-(3,5-difluorophenylacetyl)-L-isoleucinyl]-L-phenylglycine methyl ester

65 *N*-[*N*-(3,5-difluorophenylacetyl)-(S)-2-amino-2-(cyclopropyl)acetyl]-L-phenylglycine methyl ester

70 *N*-[*N*-(3,5-difluorophenylacetyl)-(S)-2-amino-2-(thien-3-yl)acetyl]-L-phenylglycine methyl ester

75 *N*-[*N*-(3,5-difluorophenylacetyl)-(S)-2-amino-2-(thien-2-yl)acetyl]-L-phenylglycine methyl ester

80 *N*-[*N*-(3,5-difluorophenylacetyl)-L-(4-fluorophenyl)glyciny]-L-phenylglycine methyl ester

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5 *N*-[*N*-(3,5-difluorophenylacetyl)-D-(4-fluorophenyl)glycinyI]-L-phenylglycine methyl ester

10 *N*-[*N*-(3,5-difluorophenylacetyl)-L-(4-methoxyphenyl)glycinyI]-L-phenylglycine methyl ester

15 *N*-[*N*-(3,5-difluorophenylacetyl)-L-phenylglycinyI]-L-phenylglycine *tert*-butyl ester

20 *N*-[*N*-(cyclopropylacetyl)-L-phenylglycinyI]-L-phenylglycine *tert*-butyl ester

25 *N*-[*N*-(cyclopentylacetyl)-L-phenylglycinyI]-L-phenylglycine *tert*-butyl ester

30 *N*-[*N*-(*tert*-butylacetyl)-L-alaninyl]-L-phenylglycinamide

35 *N*-*tert*-butyl-*N*'-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-(5-bromothien-2-yl)glycinamide

40 *N*-*tert*-butyl-*N*'-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D-(5-bromothien-2-yl)glycinamide

45 *N*-*tert*-butyl-*N*'-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylglycinamide

50 *N*-*tert*-butyl-*N*'-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-(thien-2-yl)glycinamide

55 *N*-*tert*-butyl-*N*'-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D-(thien-2-yl)glycinamide

60 *N*-*tert*-butyl-*N*'-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-(thien-3-yl)glycinamide

65 *N*-*tert*-butyl-*N*'-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D-(thien-2-yl)glycinamide

70 *N*-*tert*-butyl-*N*'-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D-phenylglycinamide

75 *N*-*tert*-butyl-*N*'-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylglycinamide

80 *N*-*tert*-butyl-*N*'-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-(5-chlorothien-2-yl)glycinamide

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5 *N*-Cyclohexyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D-4-(phenyl)phenylglycinamide

10 *N*-*tert*-butyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-3-(phenoxy)phenylglycinamide

15 *N*-(S)-(-)- α -methylbenzyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-phenylglycinamide

20 *N*-*tert*-butyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-3-(phenyl)phenylglycinamide

25 *N*-*tert*-butyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-4-(ethyl)phenylglycinamide

30 *N*-*tert*-butyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-2-(phenyl)phenylglycinamide

35 *N*-*tert*-butyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-2-(benzyl)phenylglycinamide

40 *N*-*tert*-butyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-4-(4-bromophenyl)phenylglycinamide

45 *N*-*tert*-butyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-4-(cyclohexyl)phenylglycinamide

50 *N*-*tert*-butyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-4-(4-ethylphenyl)phenylglycinamide

55 *N*-*tert*-butyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-4-(*tert*-butyl)phenylglycinamide

60 *N*-*tert*-butyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-3-(4-chlorophenoxy)phenylglycinamide

65 *N*-cyclohexyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-4-(phenyl)phenylglycinamide

70 *N*-[*N*-(3,5-difluorophenyl- α -hydroxyacetyl)-L-alaninyl]-L-phenylglycine
 tert-butyl ester

75 *N*-*tert*-butyl-*N'*-[*N*-(3,5-difluorophenyl- α , α -difluoroacetyl)-L-alaninyl]-L-phenylglycinamide

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5 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D-phenylglycine *tert*-butyl ester

10 *N*-[(S)-1-oxo-1-phenylprop-2-yl]-*N*'-(3,5-difluorophenylacetyl)-L-alaninamide

15 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-(pyrid-3-yl)glycine *tert*-butyl ester

20 [*N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-phenylglycinyl]morpholine

25 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-(2-methoxy)phenylglycine methyl ester

30 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-phenylglycine *N*-*tert*-butoxycarbonyl(hydroxyl amine) ester

35 *N*-neopentyl-*N*'-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-phenylglycinamide

40 *N*-tetrahydrofurfuryl-*N*'-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-phenylglycinamide

45 *N*-methoxy-*N*'-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-phenylglycinamide

 [*N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-phenylglycinyl]azetidine

N-iso-butyl-*N*'-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-phenylglycinamide

N-cyclopropanemethyl-*N*'-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-phenylglycinamide

N-methoxy-*N*-methyl-*N*'-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-phenylglycinamide

N-2-methylprop-2-enyl-*N*'-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-phenylglycinamide

N-(pyrid-3-yl)methyl-*N*'-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-phenylglycinamide

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5 *N*-(pyrid-4-yl)methyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-phenylglycinamide

10 *N*-furfuryl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-phenylglycinamide

15 *N*-cyclopentyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-phenylglycinamide

20 *N*-1-benzylpiperidin-4-yl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-phenylglycinamide

25 *N,N*-dimethyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-phenylglycinamide

30 *N*-2,2,6,6-tetramethylpiperidin-4-yl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-phenylglycinamide

35 *N*-2-methylcyclohexyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-phenylglycinamide

40 *N*-4-methylcyclohexyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-phenylglycinamide

45 *N*-1-ethoxycarbonylpiperidin-4-yl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-phenylglycinamide

50 *N*-methyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylglycinamide

55 *N*-*tert*-butoxy-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-phenylglycinamide

60 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-phenylglycine *N*-*tert*-butyl(hydroxylamine) ester

65 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylglycine hydrazide

70 *N*-(1-ethoxyethen-1-yl)-[*N'*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylglycine hydrazide

75 *N*-[*N*-(phenylacetyl)-L-alaninyl]-L-phenylglycine *tert*-butyl ester

80 *N*-4-(phenyl)butyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylglycinamide

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5 *N*-3-(4-iodophenoxy)propyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylglycinamide

10 *N*-6-(amino)hexyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-phenylglycinamide Hydrochloride

15 *N*-1-(phthalimido)pent-2-yl-*N'*-(3,5-difluorophenylacetyl)-L-alaninamide

20 *N*-[*N*-(3,5-difluorophenylacetyl)-L-(3,5-difluorophenyl)glycanyl]-L-(3,5-difluorophenyl)glycine methyl ester

25 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-norleucine

30 *N*-[*N*-(cyclopentaneacetyl)-L-alaninyl]-L-phenylglycine *tert*-butyl ester

35 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-4-fluorophenylglycine *iso*-propyl ester

40 *N*-(isopropyl) *N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylglycinamide

45 *N*-[*N*-(cyclopentylacetyl)-L-alaninyl]-L-phenylalanine *tert*-butyl ester

50 *N*-[*N*-(cyclopropylacetyl)-L-alaninyl]-L-phenylalanine *tert*-butyl ester

55 *N*-[*N*-(3,5-Difluorophenylacetyl)-L-alaninyl]-L-phenylglycine *iso*-butyl ester

60 *N*-[*N*-(3,5-Difluorophenylacetyl)-L-alaninyl]-D-phenylglycine methyl ester

65 *N*-[*N*-(3,5-Difluorophenylacetyl)-L-alaninyl]-L-(3- α -phenyl)proline methyl ester

70 *N*-[*N*-(3,5-Difluorophenylacetyl)-L-alaninyl]-L-azetidine methyl ester

75 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-2-amino-3-(5-chlorobenzothiophen-2-yl)acetate methyl ester

80 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-(*S*)-2-amino-3-(thiazol-4-yl)propionate *tert*-butyl ester

85 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylglycinamide *tert*-butyl ester

90 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D-(thien-2-yl)glycinamide

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N-[*N*-(3,4-dichlorophenylacetyl)-L-alaninyl]-D-phenylglycinamide
5 *N*-[*N*-(3-chlorophenylacetyl)-L-alaninyl]-D-phenylglycinamide
 N-[*N*-(3-bromophenylacetyl)-L-alaninyl]-D-phenylglycinamide
10 *N*-[*N*-(3-fluorophenylacetyl)-L-alaninyl]-D-phenylglycinamide
 N-[*N*-(4-fluorophenylacetyl)-L-alaninyl]-D-phenylglycinamide
15 *N*-[*N*-(3-methylphenylacetyl)-L-alaninyl]-D-phenylglycinamide
 N-[*N*-(4-methylphenylacetyl)-L-alaninyl]-D-phenylglycinamide
20 *N*-[*N*-(3-trifluoromethylphenylacetyl)-L-alaninyl]-D-phenylglycinamide
 N-[*N*-(3-methoxyphenylacetyl)-L-alaninyl]-D-phenylglycinamide
25 *N*-[*N*-(2-chlorophenylacetyl)-L-alaninyl]-D-phenylglycinamide
 N-[*N*-(1-naphthylacetyl)-L-alaninyl]-D-phenylglycinamide
 N-[*N*-(2-naphthylacetyl)-L-alaninyl]-D-phenylglycinamide
30 *N*-[*N*-(phenylacetyl)-L-alaninyl]-D-phenylglycinamide
 N-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D-phenylglycine
35 *N*'-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-(S)-2-amino-2-(2-furanyl)acetamide
 N'-[*N*-(3,5-difluorophenylacetyl)-D-alaninyl]-D-phenylglycinamide
40 *N*'-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylalanin-N-methylsulfonamide
 N''-methyl-*N*''-phenyl-*N*'-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-glycinamide
45 *N*''-methyl-*N*''-phenyl-*N*'-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-alaninamide

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5 *N'*-[*N*-(3,5-difluorophenylacetyl)-L-methioninyl]-L-phenylglycinamide

10 *N''*-methyl-*N''*-benzyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-glycinamide

15 *N''*-4-fluorobenzyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylglycinamide

20 *N*-[*N*-(2,3,4,5,6-pentafluorophenylacetyl)-L-alaninyl]-L-(pyrid-3-yl)glycine methyl ester

25 *N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-(pyrid-3-yl)glycine *tert*-butyl ester

30 *N*-[*N*-(3,5-difluorophenylacetyl)-L-(O-benzyl)serinyl]-L-phenylglycine methyl ester

35 *N*-[*N*-(3,5-difluorophenylacetyl)-L-threoninyl]-L-phenylglycine methyl ester

40 *N*-[*N*-(3,5-difluorophenylacetyl)-L-serinyl]-L-phenylglycine methyl ester

45 *N''*-4-methylphenyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylglycinamide

N''-tetrahydrofuryl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylglycinamide

N'-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-4-fluorophenyl-glycinamide

N'-[*N*-(3,5-difluorophenylacetyl)-L-methionyl]-L-phenylglycinamide

N-[*N*-(3,5-difluorophenylacetyl)-2-aminobutanoyl]-L-phenylglycinamide

N'-[*N*-(3,5-difluorophenylacetyl)-L-phenylglycanyl]-L-phenylglycinamide

N-[*N*-(3,5-difluorophenylacetyl)-L-valinyl]-L-phenylglycinamide

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N-[(R)- α -methylbenzyl]-N'-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylglycinamide

5 N-[1-phenyl-2-oxo-3-methylbutan-1-yl]-N'-(3,5-difluorophenylacetyl)-L-alaninamide

10 N-[1-phenyl-2-oxo-propan-1-yl]-N'-(3,5-difluorophenylacetyl)-L-alaninamide

15 N-[1-phenyl-2-oxo-pentan-1-yl]-N'-(3,5-difluorophenylacetyl)-L-alaninamide

20 N-[1-phenyl-2-oxo-2-phenyl-ethan-1-yl]-N'-(3,5-difluorophenyl-acetyl)-L-alaninamide

25 N'-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-L- α -hydroxyphenylalanine methyl ester

30 N"-[4-((2-hydroxy-4-azido)-phenyl)-NHC(O)-)butyl] N'-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylglycinamide

35 N-[(S)-1-phenyl-2-oxo-2-phenyl-ethan-1-yl]-N'-(3,5-difluorophenyl-acetyl)-L-alaninamide

40 N'-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-L-4-fluorophenylglycine *tert*-butyl ester

45 N'-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-L-4-phenylphenylglycine *tert*-butyl ester
 [N-(3,5-difluorophenylacetyl)-L-alaninyl]-L-(2,3-benzo[b]proline) methyl ester

N"-*tert*-butyl-N'-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-L-4-*n*-butylphenylglycinamide

N"-*tert*-butyl-N'-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-4-(phenylacetenyl)phenylglycinamide

N'-[N-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-phenylglycinthioamide

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5 *N*-[1,3-diphenyl-2-oxo-propan-1-yl]-*N'*-(3,5-difluorophenylacetyl)-L-alaninamide

10 *N*-[1-phenyl-2-oxo-2-cyclopentylethan-1-yl]-*N'*-(3,5-difluorophenylacetyl)-L-alaninamide

15 *N*-[1-phenyl-2-oxo-hexan-1-yl]-*N'*-(3,5-difluorophenylacetyl)-L-alaninamide

20 *N*"-*n*-hexyl-6-biotinamidyl-*N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-phenylglycinthioamide

25 *N'*-[*N*-(3,5-difluorophenylacetyl)-L-methioninyl]-L-methionine

30 *N'*-[*N*-(2-*tert*-BOC-amino)propionyl]-L-alaninyl]-L-phenylglycine methyl ester

35 *N*"-*tert*-butyl *N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-L-2-fluorophenylglycinamide

40 *N'*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]-D,L-2-phenylglycine methyl ester

45 *N*-[(S)-1-phenyl-2-oxo-3-phenylpropan-1-yl]-*N'*-(3,5-difluorophenylacetyl)-L-alaninamide

50 *N'*-[*N*-(3,5-difluorophenylacetyl)-D,L-thien-3-ylglycinyl]-D,L-2-phenylglycine

55 *N'*-[*N*-(3,5-difluorophenylacetyl)-D,L-thien-3-ylglycinyl]-D,L-2-phenylglycine *tert*-butyl ester

60 *N'*-[*N*-(3,5-difluorophenylacetyl)-L-thien-3-ylglycinyl]-L-2-phenylglycine

65 *N*-[2-hydroxy-1-(S)phenyleth-1-yl]-*N'*-[(3,5-difluorophenylacetyl)-L-phenylglycinyl]-L-alaninamide

70 *N*-[2-hydroxyeth-1-yl]-*N'*-[(3,5-difluorophenylacetyl)-L-alaninyl]-L-phenylglycinamide

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N'-[*N*-(3,5-difluorophenyl-2-oxo-acetyl)-L-alaninyl]-L-2-phenylglycine
tert-butyl ester

5 [N-(2,5-dichlorophenoxyacetyl)-L-alaninyl]-L-phenylglycine methyl ester

[N-(3,5-difluorophenoxyacetyl)-L-alaninyl]-L-phenylglycine methyl ester

10 [N-(3,4-dichlorothiophenoxyacetyl)-L-alaninyl]-L-phenylglycine methyl ester

15 [N-(3-aminopropionyl)-L-alaninyl]-L-phenylglycine *tert*-butyl ester

[N-(3-*tert*-butoxycarbonylamino)propionyl]-L-alaninyl]-L-phenylglycine
tert-butyl ester

15

The pharmaceutical compositions described above comprise a pharmaceutically inert carrier and a compound of the formula I above.

20

In formula I above, X" is preferably hydrogen and X' is preferably hydrogen or fluoro.

25

In formula I above, Z is preferably a covalent bond linking R¹ to -CX'X"-.

In formula I above, preferred R¹ unsubstituted aryl groups include, for example, phenyl, 1-naphthyl, 2-naphthyl, and the like.

30

Preferred R¹ substituted aryl groups include, for example, monosubstituted phenyls (preferably 3 or 5 substituents); disubstituted phenyls (preferably 3,5 substituents); and trisubstituted phenyls (preferably 3,4,5 substituents). Preferably, the substituted phenyl groups do not include more than 3 substituents.

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Examples of substituted phenyls include, for instance, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 4-nitrophenyl, 4-methylphenyl, 3-methoxyphenyl, 3-nitrophenyl, 3-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, 3-thiomethoxyphenyl, 3-methylphenyl, 3-trifluoromethylphenyl, 2-hydroxyphenyl, 2-methylphenyl, 2-fluorophenyl, 2-chlorophenyl, 3,4-difluorophenyl, 2,3,4,5,6-pentafluorophenyl, 3,4-dibromophenyl, 3,4-dichlorophenyl, 3,4-methylene-dioxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 2,4-dichlorophenyl, and 2,5-difluorophenyl.

Preferred R¹ alkaryl groups include, by way of example, benzyl, 2-phenylethyl, 3-phenyl-*n*-propyl, and the like.

Preferred R¹ alkyl, substituted alkyl, alkenyl, cycloalkyl and cycloalkenyl groups include, by way of example, *iso*-propyl, *n*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, -CH₂CH=CH₂, -CH₂CH=CH(CH₂)₄CH₃, cyclopropyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclohex-1-enyl, -CH₂-cyclopropyl, -CH₂-cyclobutyl, -CH₂-cyclohexyl, -CH₂-cyclopentyl, -CH₂CH₂-cyclopropyl, -CH₂CH₂-cyclobutyl, -CH₂CH₂-cyclohexyl, -CH₂CH₂-cyclopentyl, aminomethyl, N-*tert*-butoxycarbonylaminomethyl, and the like.

Preferred R¹ heteroaryls and substituted heteroaryls include, by way of example, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, fluoropyridyls (including 5-fluoropyrid-3-yl), chloropyridyls (including 5-chloropyrid-3-yl), thien-2-yl, thien-3-yl, benzothiazol-4-yl, 2-phenylbenzoxazol-5-yl, furan-2-yl, benzofuran-2-yl, thionaphthen-2-yl, 2-chlorothiophen-5-yl, 3-methylisoxazol-5-yl, 2-(thiophenyl)thiophen-5-yl, 6-methoxythionaphthen-2-yl, 3-phenyl-1,2,4-thioxadiazol-5-yl, 2-phenyloxazol-4-yl, and the like.

Preferably R² is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl and heterocyclic. Particularly preferred R² substituents include, by way of example, methyl, ethyl, *n*-propyl,

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5 *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, phenyl, 4-fluorophenyl, 3,5-difluoro-phenyl, 4-methoxyphenyl, benzyl, cyclopropyl, cyclohexyl, cyclopentyl, cycloheptyl, thien-2-yl, thien-3-yl, -CH₂CH₂SCH₃, -CH₂OCH₂φ, -CH(CH₃)OCH₂φ, -CH(OH)CH₃, -CH₂OH and the like. As noted below, R² (as well as R⁴) is preferably the side chain of an L-amino acid.

10 Preferably, R³ is hydrogen, methyl or together with R⁴ and the nitrogen to which R³ is attached forms pyrrolidin-2-yl, 2,3-dihydroindol-2-yl, piperidin-2-yl, 4-hydroxy-pyrrolidin-2-yl, 1,2,3,4-tetrahydroisoquinolin-3-yl, and the like.

15 10 Preferred R⁴ substituents include, for example, hydrogen, methyl, ethyl, *iso*-propyl, *n*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, cyclopentyl, cyclohexyl, allyl, *iso*-but-2-enyl, 3-methylpentyl, -CH₂-cyclopropyl, -CH₂-cyclohexyl, -CH₂-indol-3-yl, phenyl, *p*-(phenyl)phenyl, *m*-(phenyl)phenyl *o*-fluorophenyl, *m*-fluorophenyl, *p*-fluorophenyl, *p*-bromophenyl, *m*-methoxyphenyl, *p*-methoxyphenyl, phenethyl, benzyl, *m*-hydroxybenzyl, *p*-hydroxybenzyl, *p*-nitrobenzyl, *m*-trifluoromethylphenyl, *p*-(CH₃)₂NCH₂CH₂CH₂O-benzyl, *p*-(CH₃)₃COC(O)CH₂O-benzyl, *p*-phenylphenyl, 3,5-difluorophenyl, *p*-(HOOCCH₂O)-benzyl, 2-aminopyrid-6-yl, 4-(N-morpholino-CH₂CH₂O)-benzyl, -CH₂CH₂C(O)NH₂, -CH₂-imidazol-4-yl, -CH₂-(3-tetrahydrofuranyl), -CH₂-thien-2-yl, -CH₂-thiazol-4-yl, -CH₂(1-methyl)cyclopropyl, -CH₂-thien-3-yl, thien-3-yl, thien-2-yl, -CH₂-C(O)O-*t*-butyl, -CH₂-C(CH₃)₃, -CH₂CH(CH₂CH₃)₂, 2-methylcyclopentyl, -cyclohex-2-enyl, -CH[CH(CH₃)₂]COOCH₃, -(CH₂)₂SCH₃, -CH₂CH₂N(CH₃)₂, -CH₂C(CH₃)=CH₂, -CH₂CH=CHCH₃ (cis and trans), 20 -CH₂OH, -CH(OH)CH₃, -CH(O-*t*-butyl)CH₃, -CH₂OCH₃, -(CH₂)₄NH-Boc, -(CH₂)₄NH₂, -(CH₂)₄N(CH₃)₂, -CH₂-pyridyl (e.g., 2-pyridyl, 3-pyridyl and 4-pyridyl), pyridyl (2-pyridyl, 3-pyridyl and 4-pyridyl), -CH₂-naphthyl (e.g., 1-naphthyl and 2-naphthyl), -CH₂-(N-morpholino), *p*-(N-morpholino-CH₂CH₂O)-benzyl, benzo[b]thiophen-2-yl, benzo[b]thiophen-3-yl, 5- 25 chlorobenzo[b]thiophen-2-yl, 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl, 30

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benzo[b]thiophen-3-yl, tetrazol-5-yl, 5-chlorobenzo[b]thiophen-3-yl,
benzo[b]thiophen-5-yl, 6-methoxynaphth-2-yl, -CH₂-N-phthalimidyl,
2-methylthiazol-4-yl, and thieno[2,3-*b*]thiophen-2-yl,
5-bromothien-2-yl, 4-bromothien-2-yl, 5-chlorothien-2-yl, 3-phenoxyphenyl,
5 2-phenoxyphenyl, 4-ethylphenyl, 2-benzylphenyl, (4-ethylphenyl)phenyl, 4-*tert*-butylphenyl, 4-*n*-butylphenyl, *o*-(4-chlorophenoxy)phenyl, furan-2-yl, 4-phenylacetylenylphenyl and the like.

Preferably, R⁵ is hydrogen. However, in another embodiment, R⁴ and
10 R⁵ are fused to form a cycloalkyl group including, for example, cyclopropyl,
cyclobutyl, and the like.

One preferred X substituent is -C(O)Y. Preferably Y is hydroxy,
alkoxy or substituted alkoxy such as methoxy, ethoxy, *n*-propoxy, *iso*-propoxy,
15 *n*-butoxy, *iso*-butoxy, *tert*-butoxy, *neo*-pentoxy, benzyloxy, 2-phenylethoxy, 3-phenyl-*n*-propoxy, 3-iodo-*n*-propoxy, 4-bromo-*n*-butoxy, -ONHC(O)OC(CH₃)₃,
-ONHC(CH₃)₃ and the like. Another preferred Y group is -NR'R" where R'
and R" are as defined above. Such preferred Y groups include, by way of
example, amino (-NH₂), -NH(*iso*-butyl), -NH(*sec*-butyl), N-methylamino, N,N-dimethylamino, N-benzylamino, N-morpholino, azetidino, N-thiomorpholino,
20 N-piperidinyl, N-hexamethyleneimino, N-heptamethylene-imino, N-pyrrolidinyl,
-NH-methallyl, -NHCH₂-(furan-2-yl), -NHCH₂-cyclopropyl, -NH(*tert*-butyl),
-NH(*p*-methylphenyl), -NHOCH₃, -NHCH₂(*p*-fluorophenyl), -NHCH₂CH₂OCH₃,
-NH-cyclopentyl, -NH-cyclohexyl, -NHCH₂CH₂N(CH₃)₂, -NHCH₂C(CH₃)₃,
25 -NHCH₂-(pyrid-2-yl), -NHCH₂-(pyrid-3-yl), -NHCH₂-(pyrid-4-yl),
N-thiazolindinyl, -N(CH₂CH₂CH₃)₂, -N[CH₂CH(CH₃)₂]₂, -NHOH,
-NH(*p*-NO₂-φ), -NHCH₂(*p*-NO₂-φ), -NHCH₂(*m*-NO₂-φ), -N(CH₃)OCH₃,
-N(CH₃)CH₂-φ, -NHCH₂-(3,5-di-fluorophenyl), -NHCH₂CH₂F, -NHCH₂(*p*-CH₃O-φ),
-NHCH₂(*m*-CH₃O-φ), -NHCH₂(*p*-CF₃-φ), -N(CH₃)CH₂CH₂OCH₃,
30 -NHCH₂CH₂φ, -NHCH(CH₃)φ, -NHCH₂-(*p*-F-φ), -N(CH₃)CH₂CH₂N(CH₃)₂,
-NHCH₂-(tetrahydrofuran-2-yl), -NHCH₂(*p*-trifluoromethylphenyl),

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-NHCH₂C(CH₃)=CH₂, -NH-[(*p*-benzyl)pyrid-4-yl], -NH-[(2,6-dimethyl)pyrid-4-yl], -NH-(2-methylcyclohexyl), -NH-(4-methylcyclohexyl),
-NH-[N-ethoxycarbonyl]-piperidin-4-yl, -NHOC(CH₃)₃, -NHCH₂CH₂CH₂CH₂-φ,
-C(O)NH(CH₂)₃O-(*p*-CH₃)φ, -C(O)NH(CH₂)₆NH₂, -NH-(tetrahydrofuran-2-yl),
5 -N(CH₃)φ, -NH(CH₂)₄NHC(O)-(2-hydroxy-4-azido)-phenyl, -NH(CH₂)₆-
(biotinamidyl), and the like.

Another preferred Y group is an alkyl group such as methyl, ethyl,
iso-propyl, *n*-propyl, *iso*-butyl, *n*-butyl, *sec*-butyl, *tert*-butyl,
10 -CH₂CH₂CH(CH₃)₂, -CH₂-pyridy-2-yl, -CH₂-pyridy-3-yl, -CH₂-pyridy-4-yl,
-CH₂-fur-2-yl, and the like; a substituted alkyl group such as benzyl; a
cycloalkyl group such as cyclopentyl; and an aryl group such as phenyl.

Still another preferred Y group is -NHSO₂-R where R is selected from
15 alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, aryl, heteroaryl
and heterocyclic. Such groups are exemplified by NH-SO₂-CH₃.

Preferred Y' groups include a substituted alkyl group such as
-CH₂OH, -CH(OH)CH₂CH₂CH(CH₃)₂, -CH(OH)φ, -CH(OH)CH₂C(O)OCH₃,
20 -C(OH)(CH₃)₂, -CH₂OCH₃, -CH₂OC(O)OCH₃, -CH₂OC(O)C(CH₃)₃, and the
like.

Preferred compounds for use in the methods of this invention include
those set forth in the tables below: